Overview: Person Centered Standard and Pragmatic Clinical trial Designs

September 29, 2025

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YaleNewHavenHealth
Smilow Cancer Hospital

Yale CANCER CENTER
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Disclosures: Roy S. Herbst, MD, PhD

Consulting
AstraZeneca; Candel Therapeutics, Inc.; Checkpoint Therapeutics; DynamiCure Biotechnology, LLC; Genentech; Gilead; I-Mab Biopharma; Immune-Onc Therapeutics, Inc.; Johnson and Johnson; Loxo Oncology;NextCure; Novartis; Pfizer; Regeneron Pharmaceuticals;

Research Support
AstraZeneca; Eli Lilly and Company; Genentech/Roche; Merck and Company

Board Member (non-executive/ independent)
Immunocore

JAMA Network

JAMA | JAMA Network

October 2023, Chicago

JAMA Summit | Clinical Trials

THE PROBLEM

JAMA

Special Communication | Integrating Clinical Trials and Practice FREE

The Integration of Clinical Trials With the Practice of Medicine

Repairing a House Divided

Derek C. Angus, MD, MPH[1,2]; Alison J. Huang, MD, MAS[3]; Roger J. Lewis, MD, PhD[1,4] ; et al

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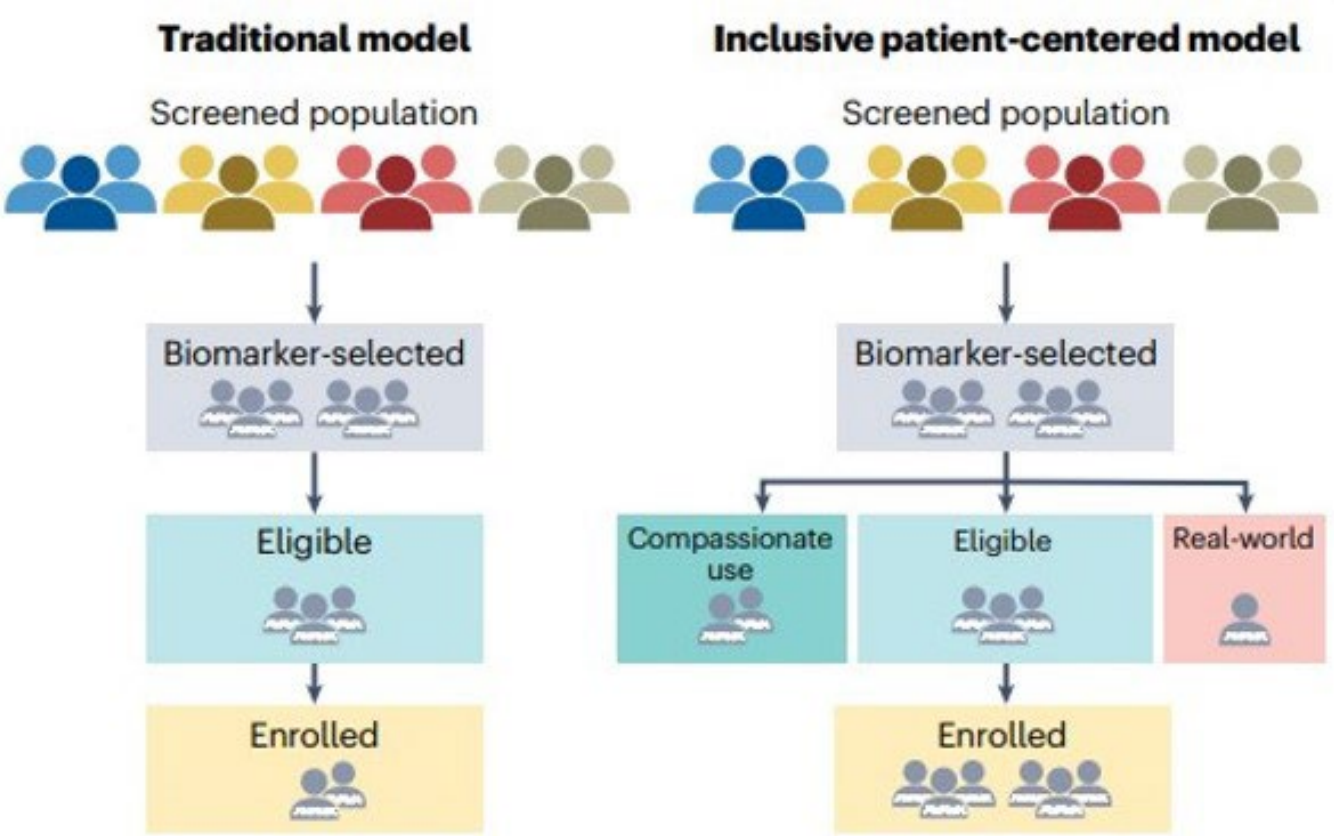
News & views

Cancer therapy

https://doi.org/10.1038/s41591-023-02466-6

Precise, pragmatic and inclusive: the modern era of oncology clinical trials

Michael J. Grant & Sarah B. Goldberg


Traditional model
Screened population
Biomarker-selected
Eligible
Enrolled
Inclusive patient-centered model
Screened population
Biomarker-selected
Compassionate use
Eligible
Real-world
Enrolled

JNCI: Journal of the National Cancer Institute, 2025, 117(7), 1305–1310
https://doi.org/10.1093/jnci/djae279
Advance Access Publication Date: December 12, 2024
Commentary

Optimizing public-private partnerships to support clinical cancer research

Roy S. Herbst, MD, PhD*,[1], Gideon Blumenthal, MD[2], Samir N. Khleif, MD[3], Scott M. Lippman, MD[4], Neal J. Meropol, MD[5], Kristen Rosati, JD[6], Lawrence N. Shulman, MD[7], Heind Smith, MS[8], Meina Wang, PhD[1], Robert A. Winn, MD[9], Richard L. Schilsky, MD[10]

Box 1

National Cancer Institute (NCI) definition of PPP: A public-private partnership (PPP) is an agreement to work in concert with a nonfederal party or parties to advance mutual interests to improve health.

Purpose of PPPs: Improve understanding of cancer; accelerate progress in cancer research; foster collaboration to advance cancer research.

Guiding principles of PPPs:

- Should be undertaken for the public good
- Should address important scientific questions of high priority with clearly articulated goals
- Must be scientifically meritorious and address unmet needs
- Should leverage partner resources to accomplish the scientific goals that would not be possible by any party alone

Plan For the Talk

1. Evolution of Lung-MAP- A Master Protocol as a Public Private Partnership)

2. The Lung Pragmatica Trial

3. Thoughts for the Future

Plan For the Talk

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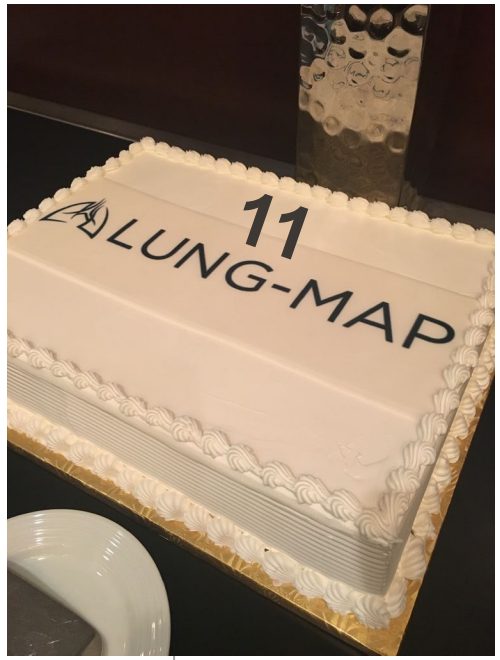

Design of a Disease-Specific Master Protocol

2012 Friends of Cancer Research / Brookings Institution
Conference on Clinical Cancer Research

ISSUE BRIEF

Conference on Clinical Cancer Research

November 2012

Design of a Disease-Specific Master Protocol

Roy Herbst, Chief of Medical Oncology, Yale Cancer Center
Eric Rubin, Vice President, Clinical Research Oncology, Merck
Lisa LaVange, Director, Office of Biostatistics, CDER, FDA
Jeffrey Abrams, Associate Director, Cancer Therapy Evaluation Program, NCI
David Wholley, Director, The Biomarkers Consortium, FNIH
Karen Arscott, Patient Advocate, Lung Cancer Alliance
Shakuntala Malik, Medical Officer, FDA

Introduction

Despite several impressive therapeutic advances in recent years, cancer remains the second-leading cause of death in the United States, and effective new therapies are still desperately needed. Developing a potential therapy from the initial discovery stage through clinical testing and regulatory review is a complicated, expensive, and often inefficient process that can take up to 15 years. Included among the many challenges of drug development are the difficulties in recruiting cancer patients to clinical trials, the extensive bureaucratic processes required to initiate any clinical trial, and lengthy regulatory review. Modernizing this process with innovative approaches and new clinical trial designs is of high importance.

FRIENDS of CANCER RESEARCH

http://www.focr.org/events/design-lung-cancer-master-protocol

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Lung-MAP Mission and Vision

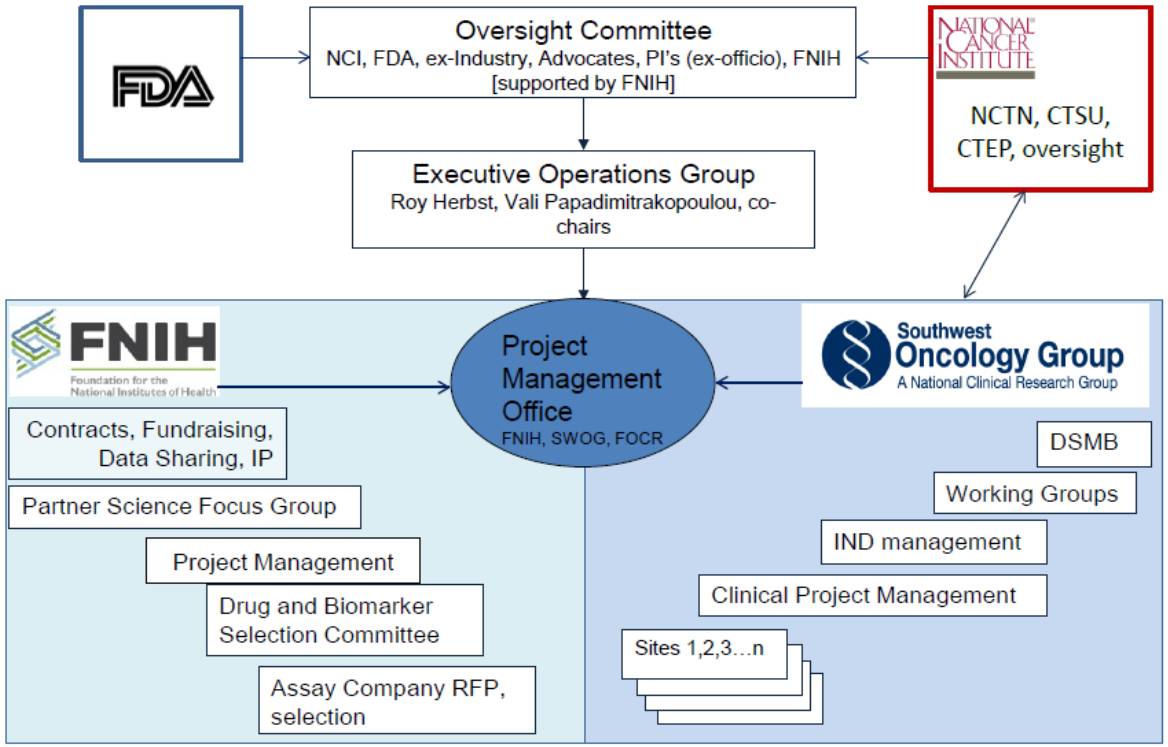
Mission

Lung-MAP aims to transform metastatic NSCLC treatment through precision medicine, tailoring therapies to each tumor's genetic makeup. Our mission is to enhance patient outcomes by partnering with key stakeholders to expedite innovative research and clinical application, while leveraging patient data to inform future advancements.

Vision

We envision a future where personalized care for metastatic NSCLC, rooted in precision medicine and the latest research, is accessible to all. Our goal is to continually foster a collaborative environment that fosters breakthroughs, making lung cancer a manageable condition while eliminating disparities in care and treatment outcomes.

It takes a Village: Teamwork breeds success



FOUNDATION MEDICINE

AstraZeneca

Bristol Myers Squibb

abbvie

Pfizer

Genentech BIOONCOLOGY

AMGEN

Lilly

MedImmune

MERCK

CLOVIS ONCOLOGY

LOXO ONCOLOGY
Wholly owned subsidiary of Eli Lilly and Company

ImmunityBio

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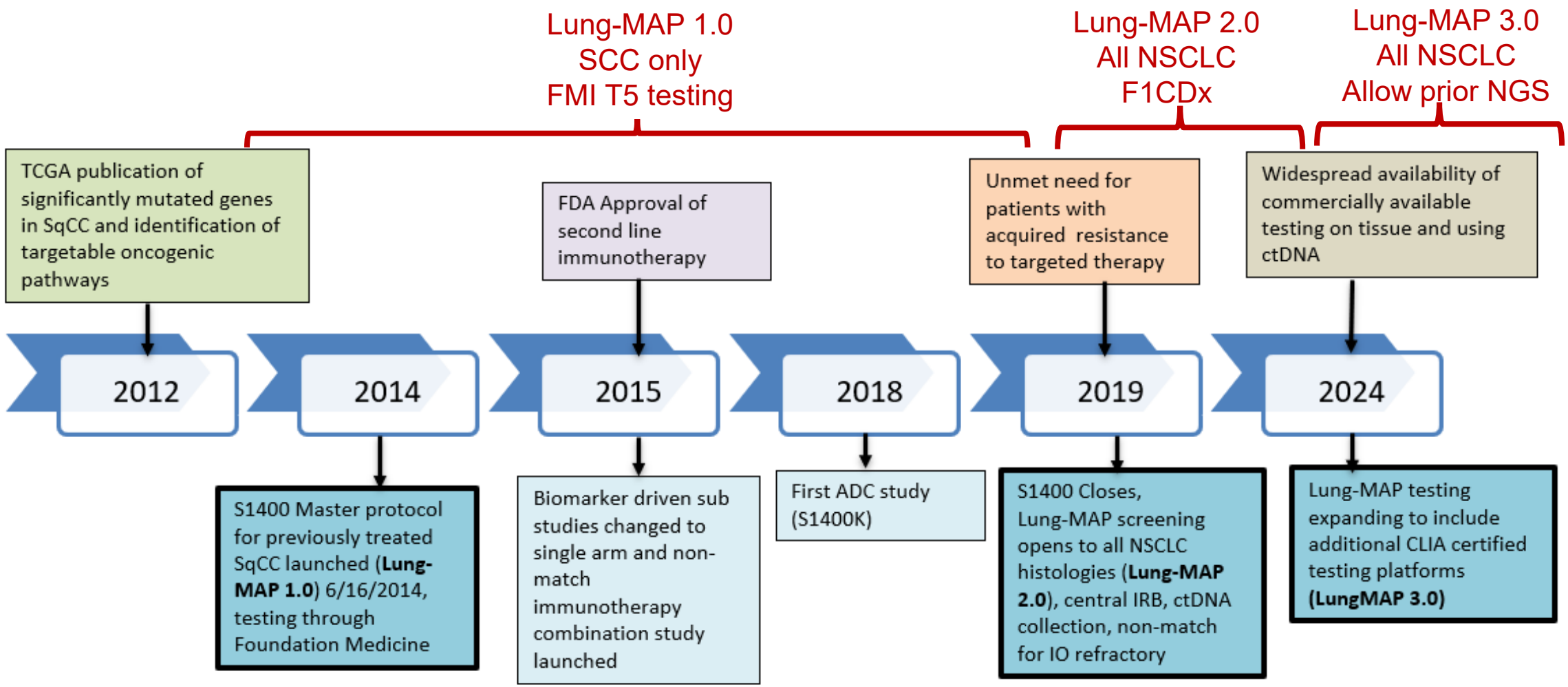
LUNG-MAP

SWOG CANCER RESEARCH NETWORK

Lung-MAP Evolution (2014-2024)

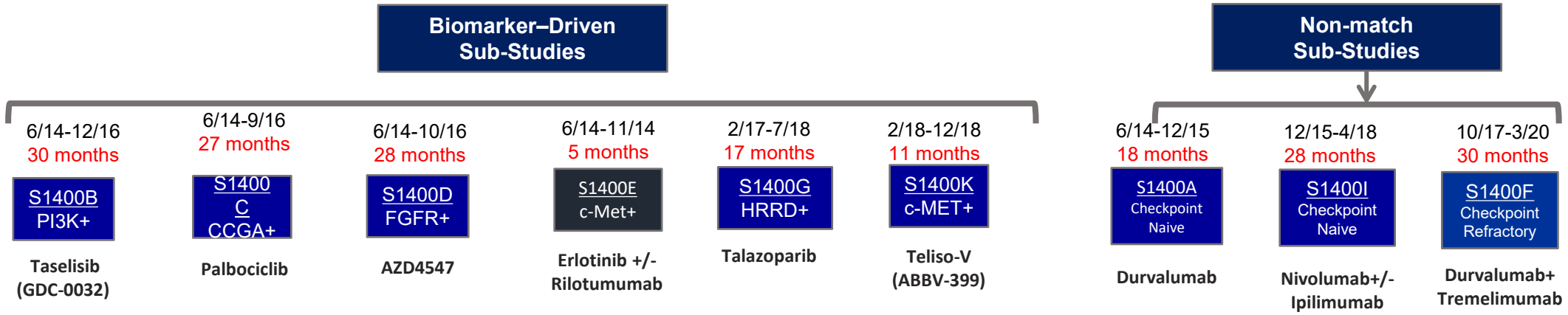


Slide from Dr. Mary Redman, AACR 2025

Lung-MAP 1.0 Sub-studies

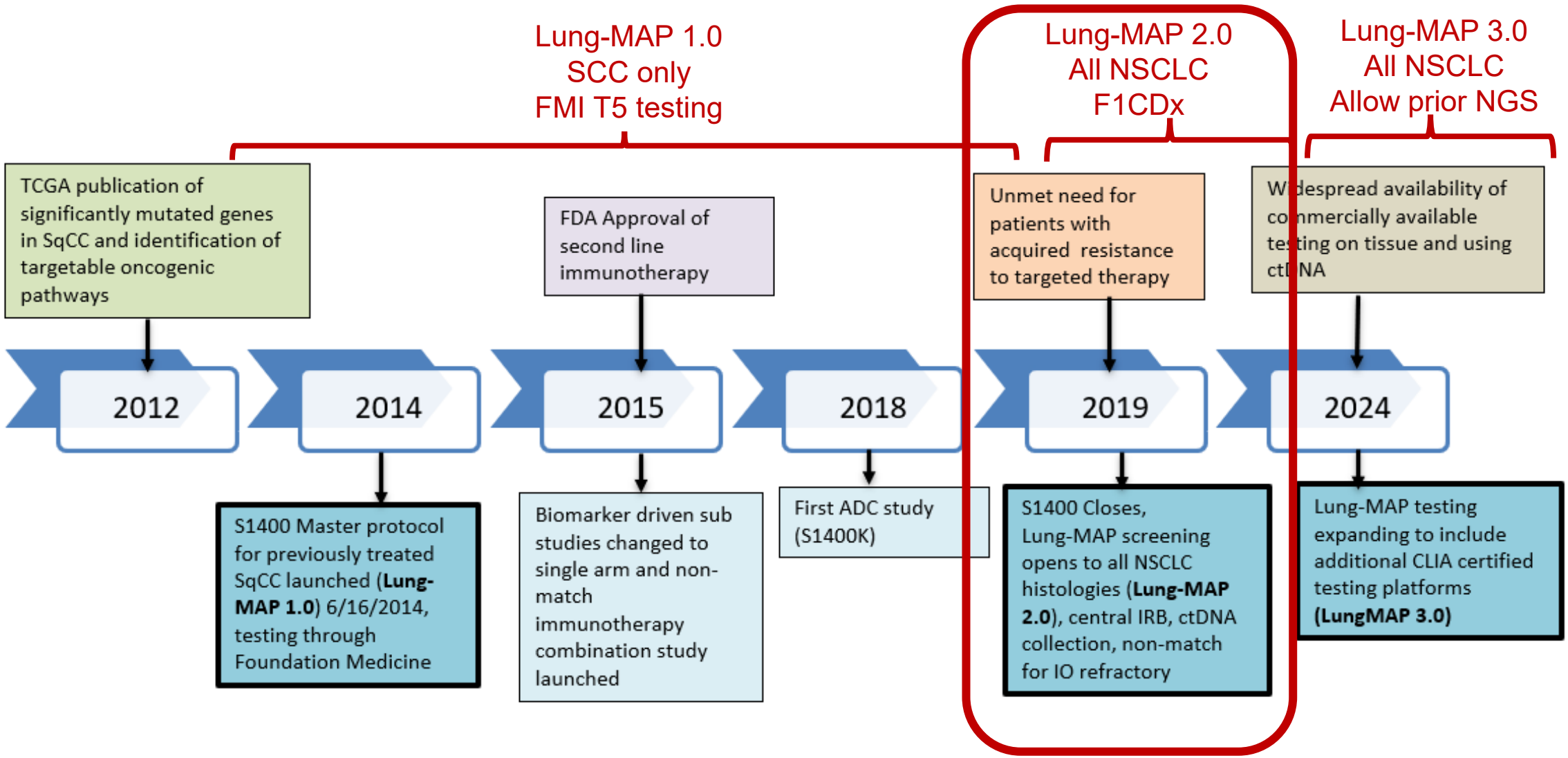
Previously-Treated Squamous Cell Lung Cancer

Foundation Medicine T5 Platform

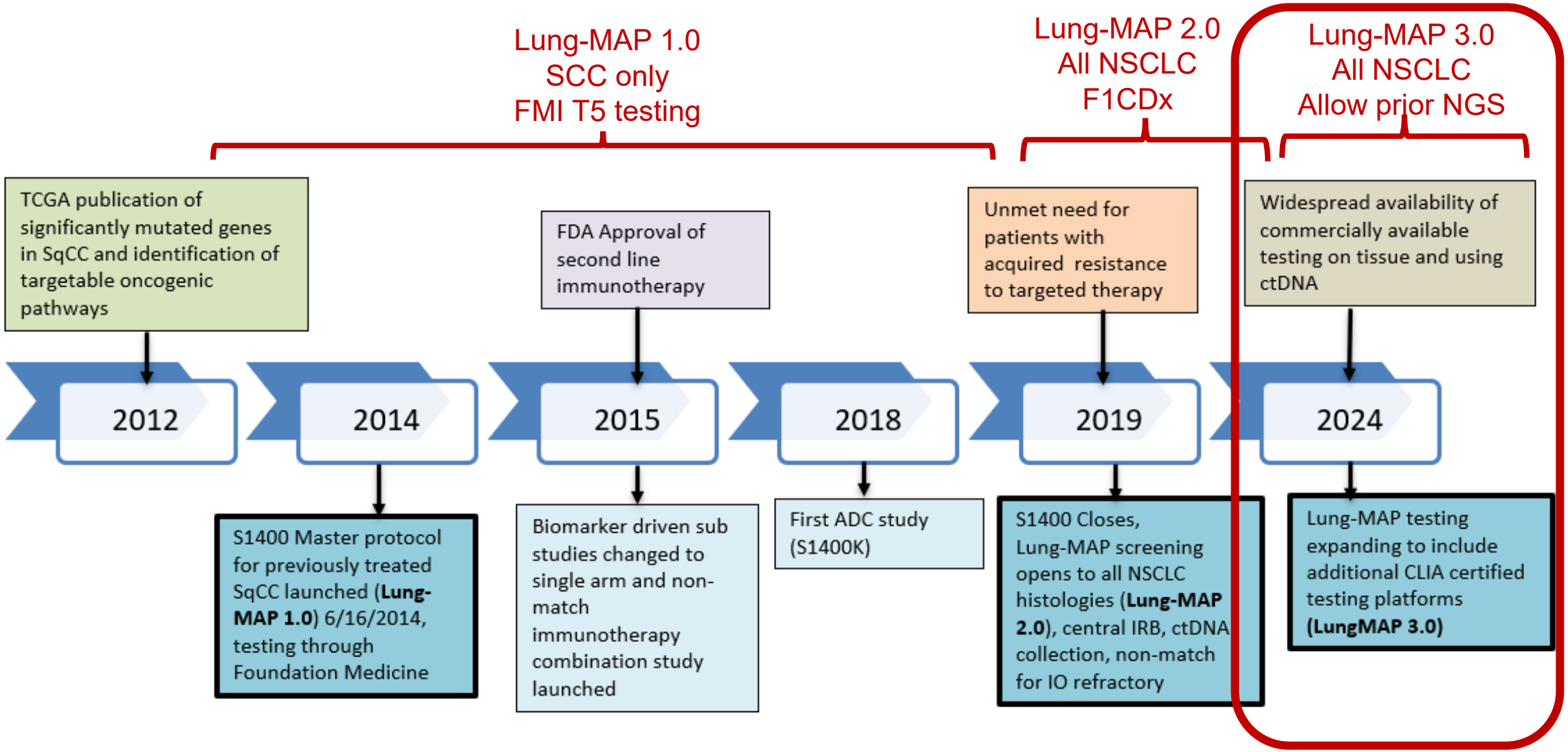


Study	S1400B	S1400C	S1400D	S1400E	S1400G	S1400K		S1400A	S1400I	S1400F
Enrolled Sample Size	31 taselisib 8 doce	37 palbo 17 doce	35 AZD4547 10 doce	9 total	51	28		78 durva, 38 doce	275	PR: 28 AR: 30
Primary Analysis	ORR: 5%	ORR: 6%	ORR: 7%	N/A	ORR: 4%	ORR: 9%		ORR: 14%	OS HR: 0.87 (0.66-1.16)	PR: 7%, AR: 0%
Study outcome	Closed at interim			Closed d/t external data	Closed at interim					

Lung-MAP Evolution (2014-2024)



Lung-MAP Evolution (2014-2024)



Lung-MAP Summary

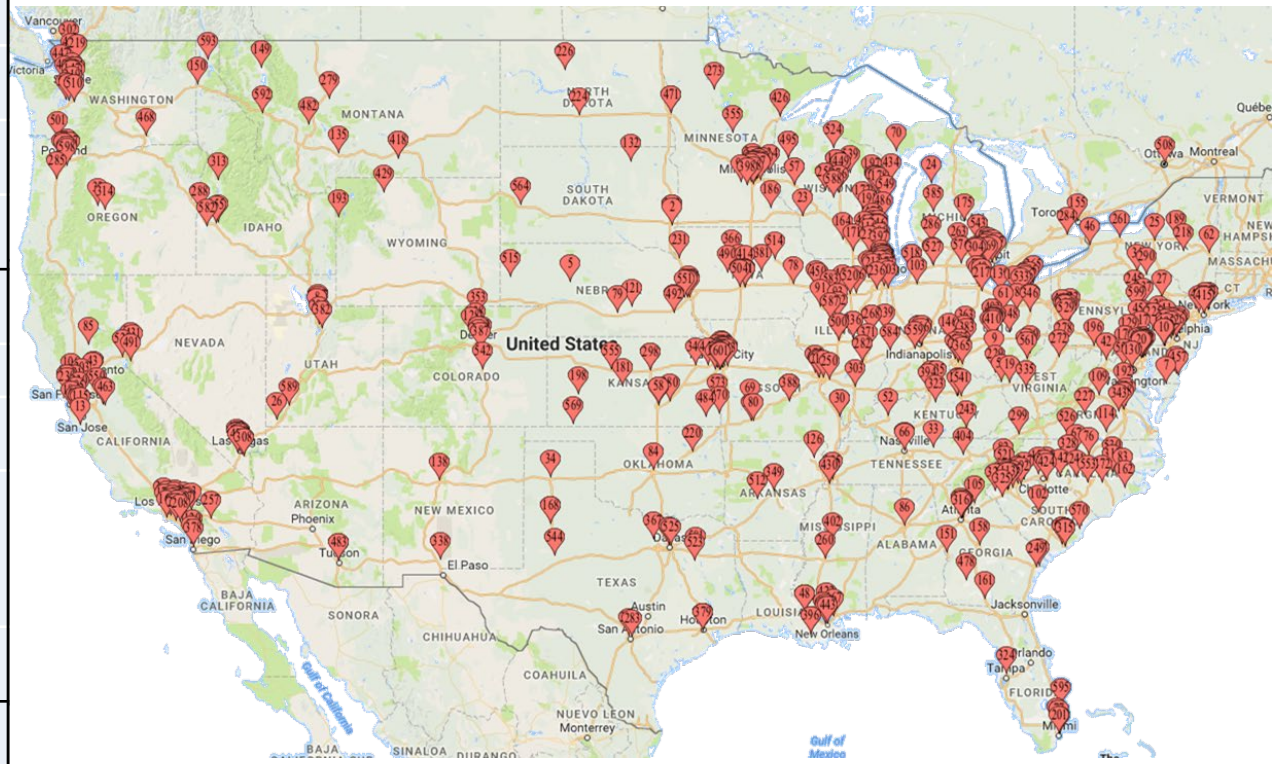
	S1400	LUNGMAP
Dates Open	June 2014 – Jan 2019 (4.58 years)	Jan 2019 – Present (5 years)
Sub-Studies Activated	9	10
Biomarker-Driven	6	7
Non-Match	3	3
Screening Registrations	1864	3698
Sub-Study Registrations	655	500

Total Screening Registrations = 5482

Total Sub-study Registrations = 1155

Where are we now?

As of 8/11/25	Total	S1400	LUNGMAP
Screening Registrations	**5562**	**1864**	**3698**
Screened at PD	2423	1127	1296
Pre-screened	3130	737	2393
Treatment-naïve	9	na	9
Sub-study Assignments	**3424**	**1484**	**1940**
Among Screened at PD	2065	996	1069
Among Pre-screened	1221	414	807
Additional Assignments after PD on a Sub-study	129	74	55
Sub-study Registrations	**1209**	**690**	**519**



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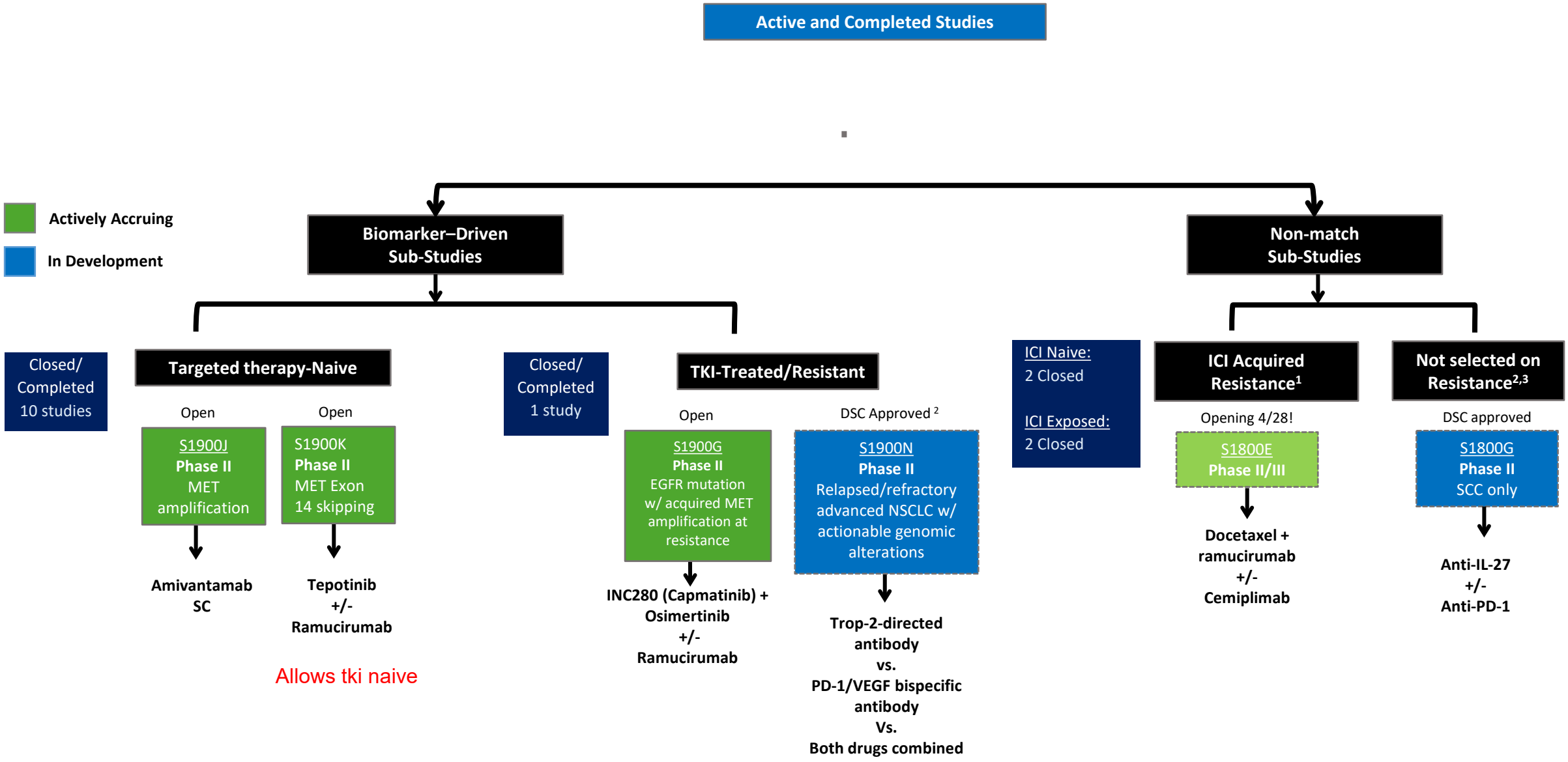
Current Lung-MAP Schema



Improved clinical trial diversity

Riha Vaidya, PhD

Mary Redman, PhD

	Lung-MAP (N=3,556)	SWOG NSCLC (N=2,215)	US NSCLC Population
Age ≥ 65 years	57.2%	46.3% *	69.8% *
Female	38.6%	47.2% *	46.0% *
Race: Black	9.2%	8.2%	14.1% *
Race: Asian/Pacific Islander	2.8%	5.1% *	4.8% *
Race: Native American	0.5%	0.4%	0.5%
Ethnicity: Hispanic	2.4%	3.8% *	5.1% *
Rural residence	17.3%	14.4% *	-- §
Areas with highest social needs	42.2%	36.7% *	-- §
Medicaid/No Insurance (if age < 65 years)	27.6%	17.8% *	-- §

* Difference versus Lung-MAP statistically significant ($p<0.01$)

§ No population-level data available for geographic/SES comparisons

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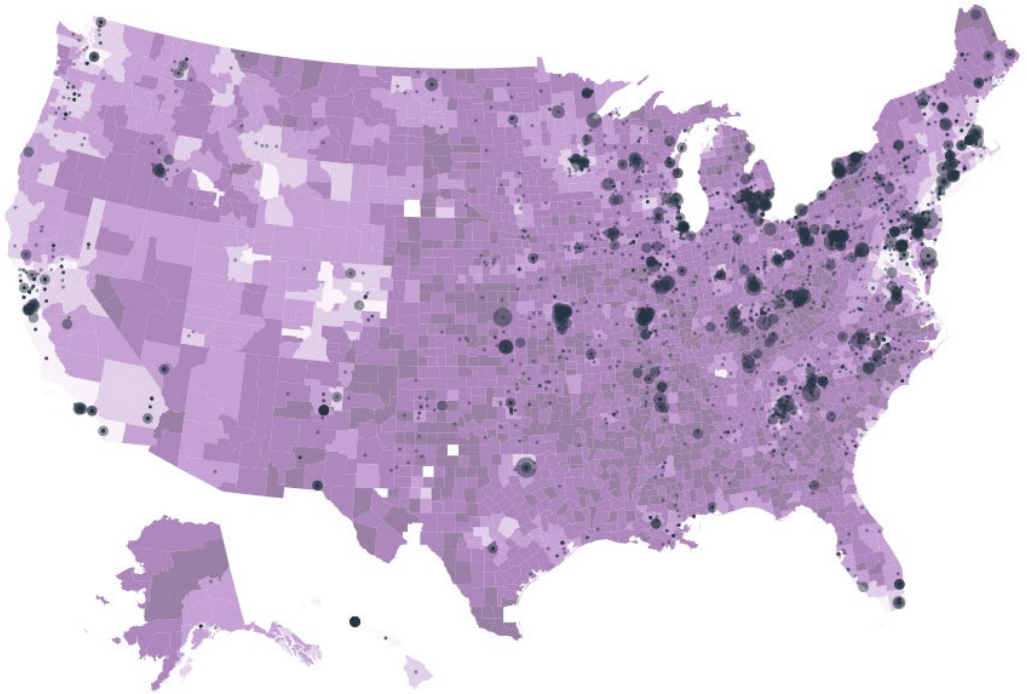
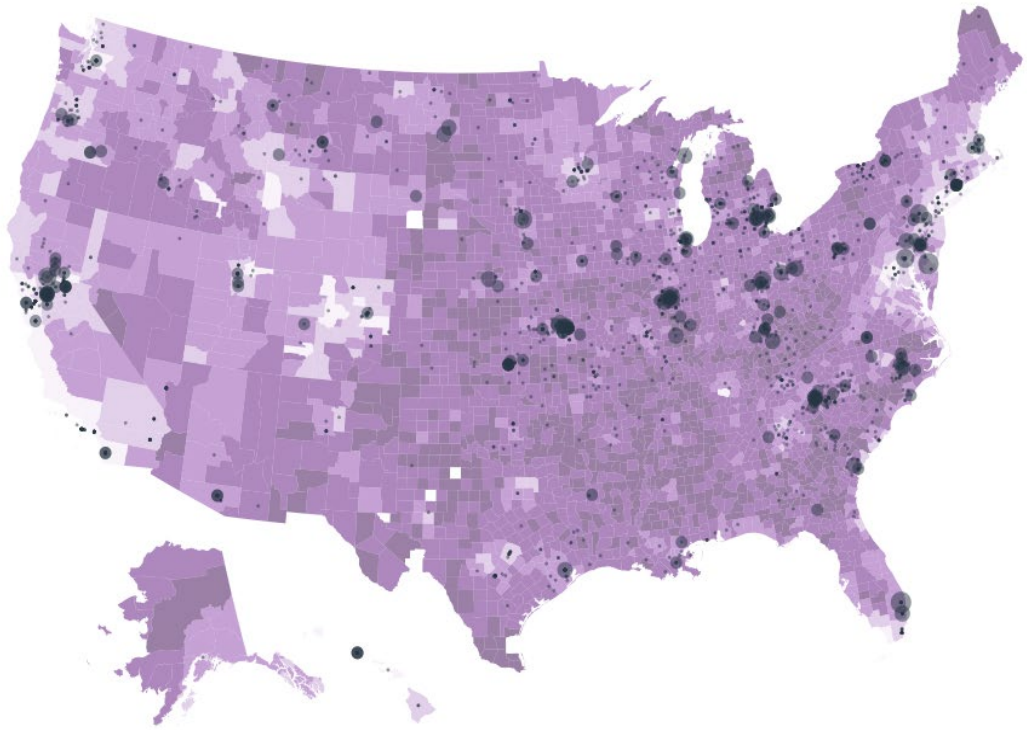
Enrollment by Area Deprivation (Rural)

LUNGMAP Accruals 1/1/2014 - 12/31/2020



NSCLC Studies Accruals 1/1/2001 - 12/31/2020



Benefits of Lung-MAP

- Working within the NCI's National Clinical Trials Network (NCTN), Lung-MAP:
  - Provides broad access to both academic and community-based clinical sites, with the screening protocol now open at more than 800 sites nationally and roughly one-half of enrollment coming from community-based sites.
    - The access to diverse populations enables the enrollment of a representative group of patients.
    - The success of Lung-MAP's approach to ensuring broadly representative enrollment has been documented in several recent publications.
  - Reduces the complications of individual contracting with sites.
  - Builds on the NCTN's infrastructure, offering opportunities for smaller companies that may have fewer resources.

Some of Lung-MAP's industry partners have included ...

abbvie

AMGEN

AstraZeneca

Bristol Myers Squibb

CLOVIS ONCOLOGY

FOUNDATION MEDICINE

Genentech BIO ONCOLOGY

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Benefits of Lung-MAP

- Facilitates testing novel agents or combinations in non-matched and matched biomarker study designs within NSCLC.
- Offers a range of study platform options.
- Collects biospecimen resources and screening data that can be used in exploratory studies.
- Offers access to leading lung cancer researchers.
- Facilitates interactions with the FDA.
- Provides drug distribution to participating sites that is managed through the NCI.
- Provides a well-organized trial development and project management system, utilizing SWOG Operations, SWOG Statistics and Data Management Center, and FNIH, to create a streamlined process for study activation.
- Provides partnership with Friends of Cancer Research who engages with advocacy organizations, offers critical patient insight on major trial decisions, and manages communications to patient advocate partners and the lung cancer community.

Some of Lung-MAP's industry partners have included ...

ImmunityBio

Lilly

LOXO ONCOLOGY
Wholly owned subsidiary of Eli Lilly and Company

MedImmune

MERCK
INVENTING FOR LIFE

NOVARTIS

Pfizer

1800A: ASCO 2022

Karen Reckamp, MD, MS

Konstantin H. Dragnev, MD

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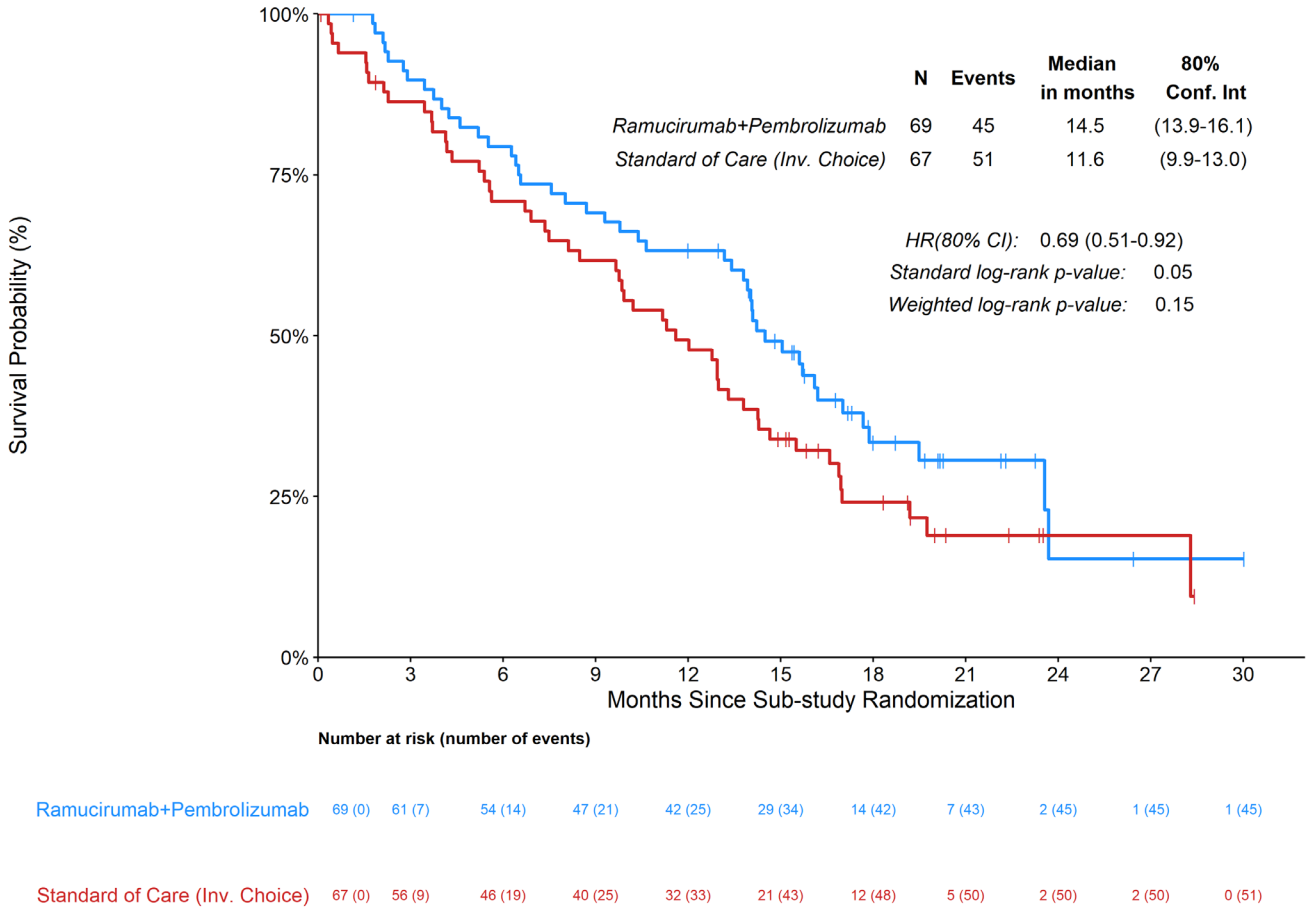
Overall survival: IO Combo hit the endpoint
Ramucirumab and pembrolizumab in previously treated advanced NSCLC



Median OS for RP 14.5 months v. SOC 11.6 months

HR= 0.69; SLR p-value 0.05

Standard of care therapy received:

- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

Plan For the Talk

1. The Birth and Evolution of Lung-MAP- A Master Protocol (A Public Private Partnership)

2. The Lung Pragmatica Trial

3. Thoughts for the Future

S2302 Pragmatica-Lung Development Timeline

Pragmatica-Lung

A real-world clinical trial for patients whose non-small cell lung cancer has returned after chemo- and immuno-therapy

Jan 2022

LUNG-MAP S1800A Data available

2022 ASCO ANNUAL MEETING #ASCO22

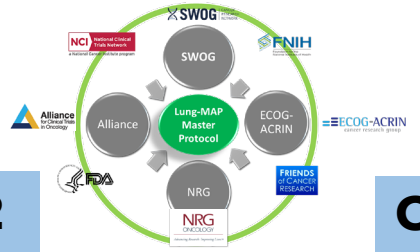
Feb 2022

ASCO abstract submitted

June 2022

Journal of Clinical Oncology

S1800A ASCO presentation/JCO publication



July 2022

Discussions start for Pragmatica-Lung

Oct 2022

FDA grants BTD for pembro/ram

S2302 Pragmatica-Lung Activation 200 days from concept to activation

Mar 2023

Completed Accrual

Dec 2024

Accrual rate >50/month

SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network | NCI Community Oncology Research Program

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Reckamp et al. ASCO 2025 abstract 110[6]

Background/Overview

- Effective therapy following frontline ICI for NSCLC is needed with limited FDA-approved options and studies are becoming more complex
- Increasing awareness that clinical research needs to adjust to enroll a generalizable population that reflects the real world
- S1800A , Phase II randomized study of ramucirumab plus pembrolizumab versus standard of care—**Overall survival was significantly improved with a hazard ratio 0.69 (80% CI; 0.51-0.92)**, median OS of 14.5 and 11.6 months, for pembrolizumab and ramucirumab vs. standard of care, respectively.
- **Pembrolizumab and ramucirumab with well known safety and efficacy profiles**
- Design a simple trial to answer the specific question of overall survival benefit (challenge: 12-page protocol and 5-page consent)
- **Achievement 47-page protocol and 11-page consent**

Pragmatica

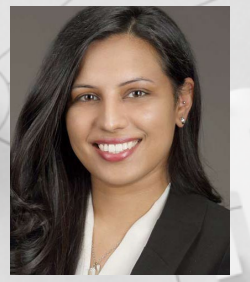
Breakthrough Designation Under Review

Working closely with FDA, NCI and NCTN partners on a Pragmatic trial

Pragmatica

A real-world clinical trial for patients whose non-small cell lung cancer has returned after immunotherapy

Richard Pazdur, MD



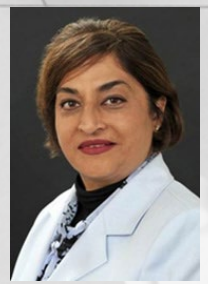
Harpreet Singh, MD

Karen Reckamp, MD, MS

Konstantin Dragnev, MD

Mary Redman, PhD

Ellen Sigal, PhD



Shakun Malik, MD

Jhanelle Gray, MD

Roy Herbst, MD PhD

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LUNG-MAP

Lilly MERCK

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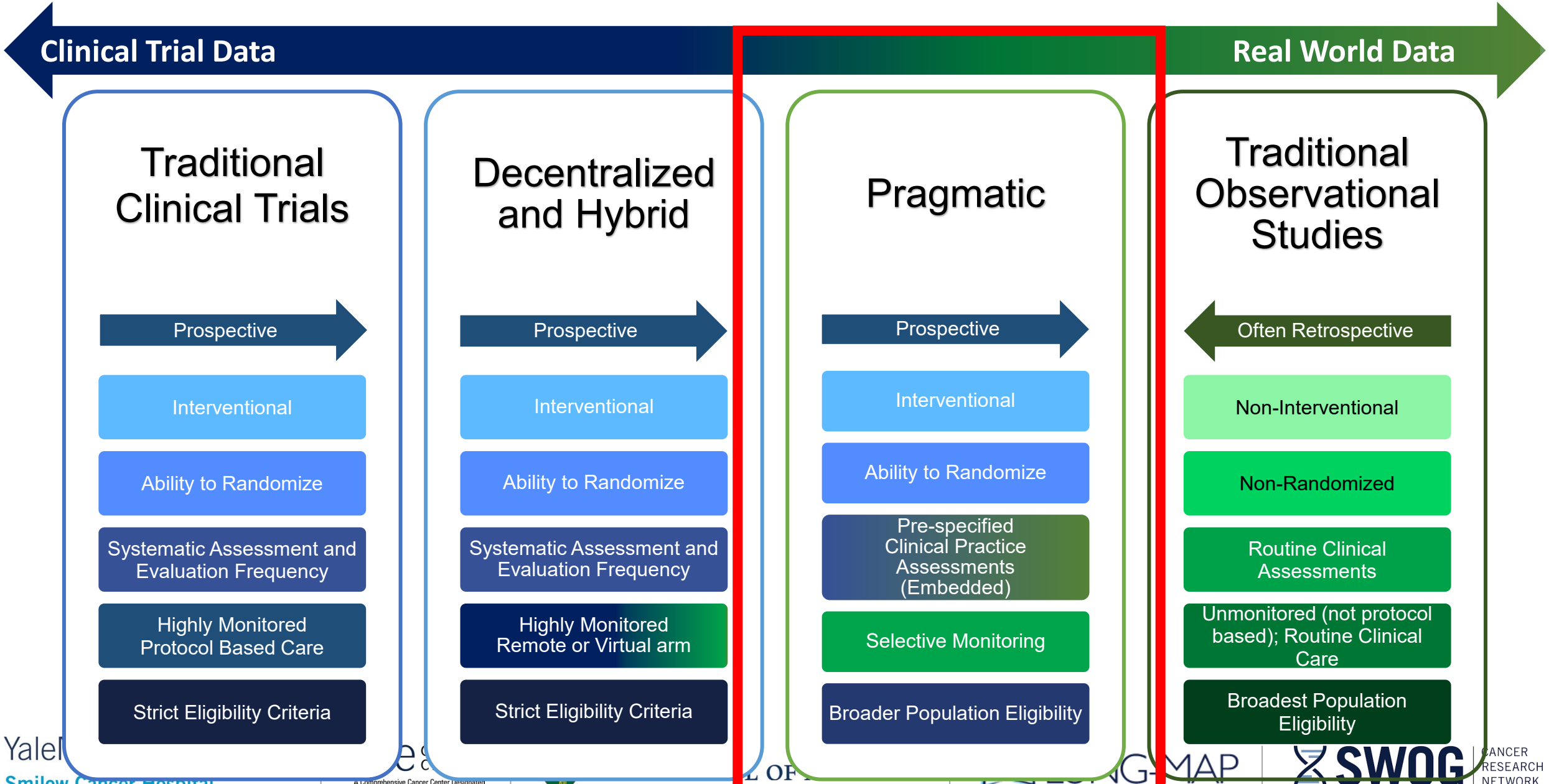
Clinical Evidence Generation Continuum



Regular Trial

Pragmatic Trial

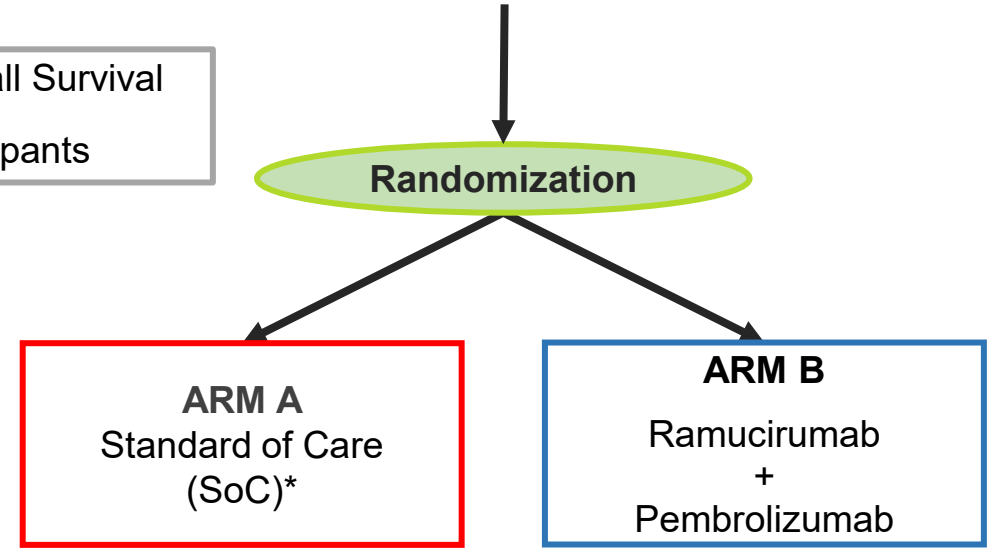
S2302 Pragmatica-Lung Schema

NCT05633602

Previously treated Stage IV or recurrent non-small cell lung cancer

Primary endpoint: Overall Survival

Accrual Goal: 800 participants



*SoC treatment is to be determined by the treating investigator and participant. It is recommended that the choice of SoC drug(s) is based on NCCN guidelines for a "systemic therapy for advanced or metastatic disease-subsequent."

Trial activation: March 6, 2023

Accrual completed: 838 participants (12/20/24)

Objectives

- **Primary study objective:** To compare **overall survival (OS)** between participants previously treated with platinum-based chemotherapy and immunotherapy for Stage IV or recurrent NSCLC randomized to pembrolizumab and ramucirumab versus SOC.
- **Secondary study objective:** To summarize reports of serious and unexpected high-grade (≥ Grade 3) treatment-related **adverse events** determined by the treating physician within each treatment arm.

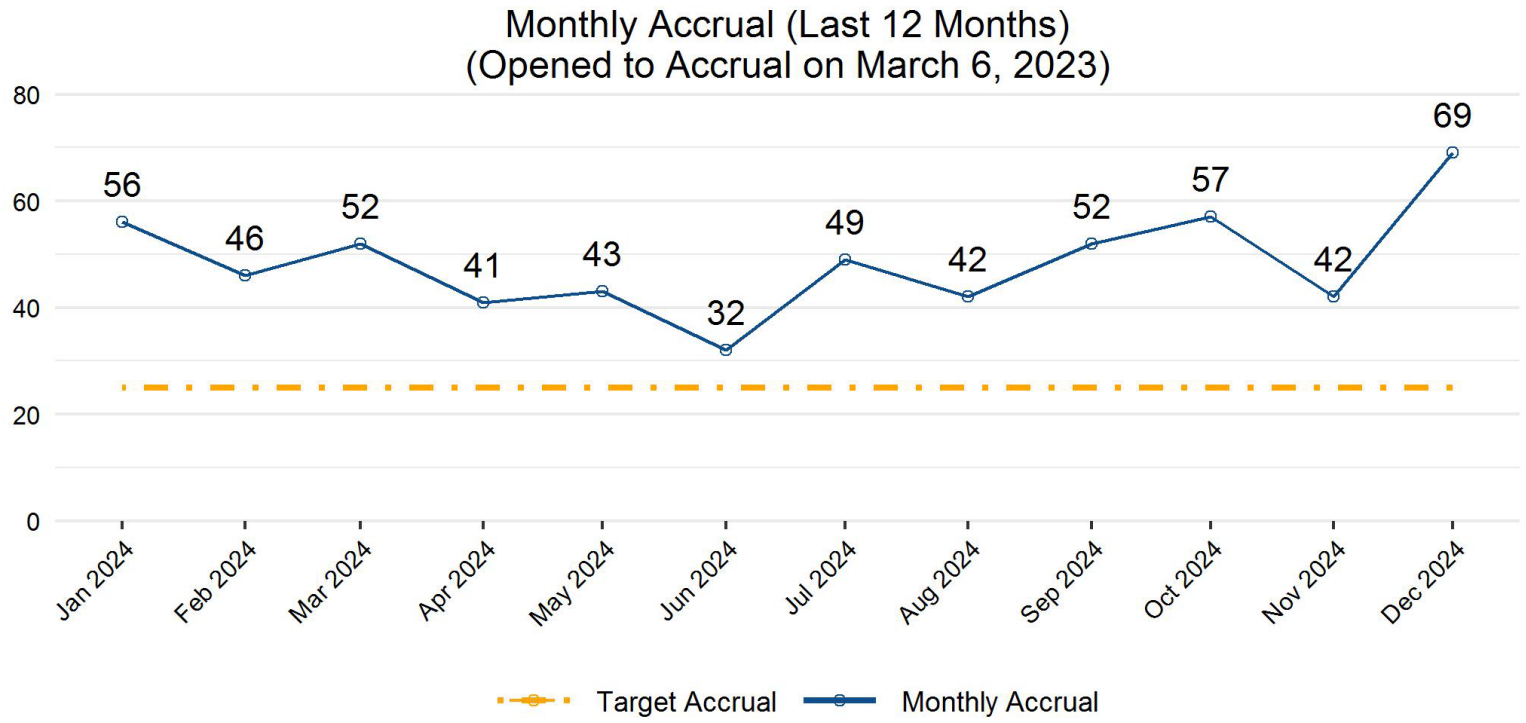
Dragnev, et al. ASCO 2025, abstract LBA8671; Reckamp et al. ASCO 2025 abstract 11016

S2302 Race, Ethnicity and Rural or Urban

	S2302: N = 838		S1800A: N=136		Census 2023 est.	Population ≥65
Race	#	%	#	%	%	%
White	652	78%	118	87%	75.5	76
Black/African American	112	13%	11	8%	13.6	12
Native Hawaiian/Other Pacific Islander	6	1%	0	0%	0.3	0.1
American Indian/Alaska Native	5	1%	1	1%	1.3	0.6
Asian	32	4%	3	2%	6.3	4.6
More Than One Race	4	<1%	1	1%	3	0.8
Unknown	27	3%	2	2%	-	-
Ethnicity	#	%	#	%	%	%
Hispanic/LatinX	32	4%	2	2%	19.1	9
Urban or Rural Sites	#	%	#	%	%	%
Not Matched	4	<1%	0	0%	-	-
Rural	119	14%	22	16%	-	-
Urban	715	85%	114	84%	-	-

Dragnev, et al. ASCO 2025, abstract LBA8671; Reckamp et al. ASCO 2025 abstract 11016; Reckamp et al. J Clin Oncol 40:2295-2306, 2022; Carrizosa D, et al. ASCO 2024, abstract 11019.

S2302 Pragmatica-Lung—Rapid Accrual

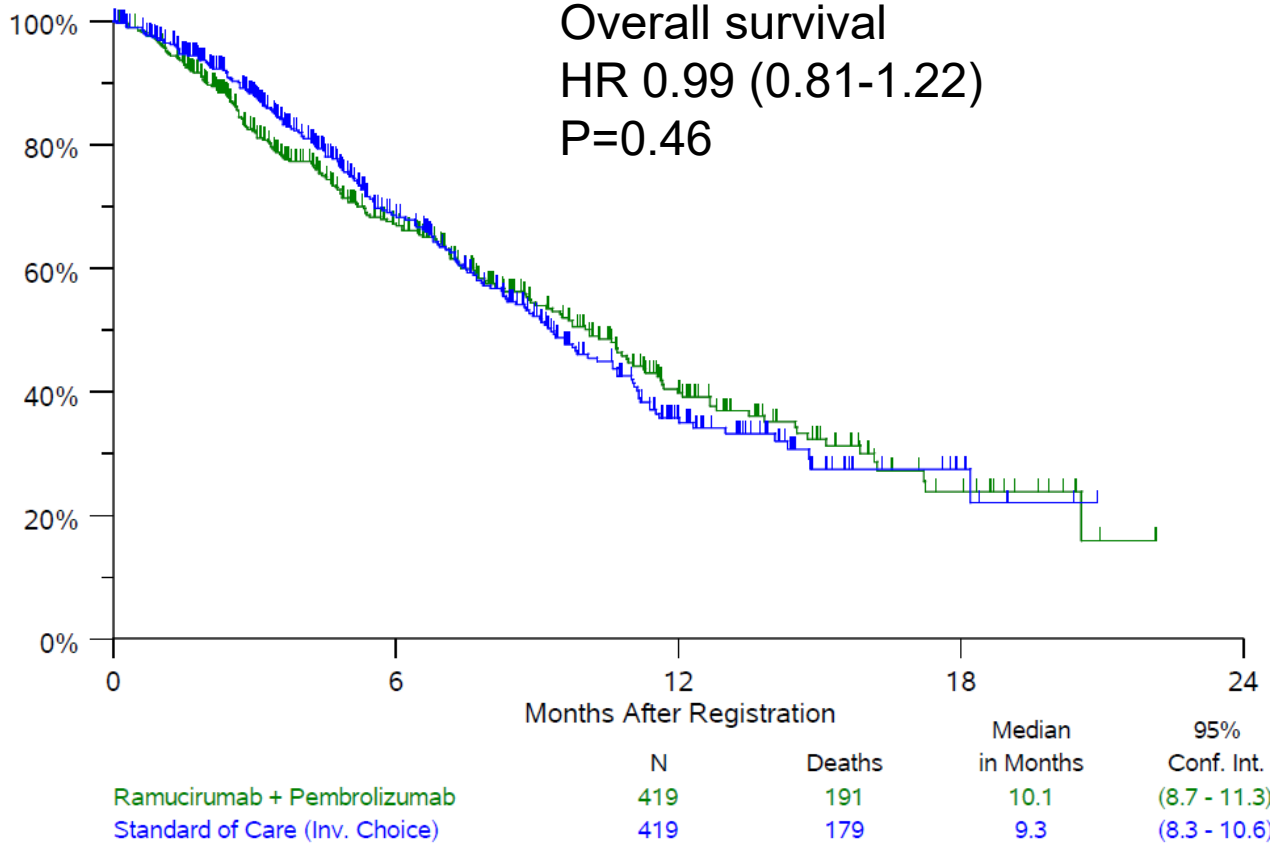


- First patient enrolled 03/14/23
- 667 sites have the study open, 252 have enrolled a participant
- Only ~ 1% of pts do not meet eligibility (typically, this is around 10%)

- Target accrual: 29 pts/month
- Actual: average over 50 pts/month in last 6 months

Pragmatica-Lung
A real-world clinical trial for patients whose non-small cell lung cancer has returned after chemo- and immuno-therapy

Overall survival



	N	Deaths	Median in Months	95% Conf. Int.
Ramucirumab + Pembrolizumab	419	191	10.1	(8.7 - 11.3)
Standard of Care (Inv. Choice)	419	179	9.3	(8.3 - 10.6)

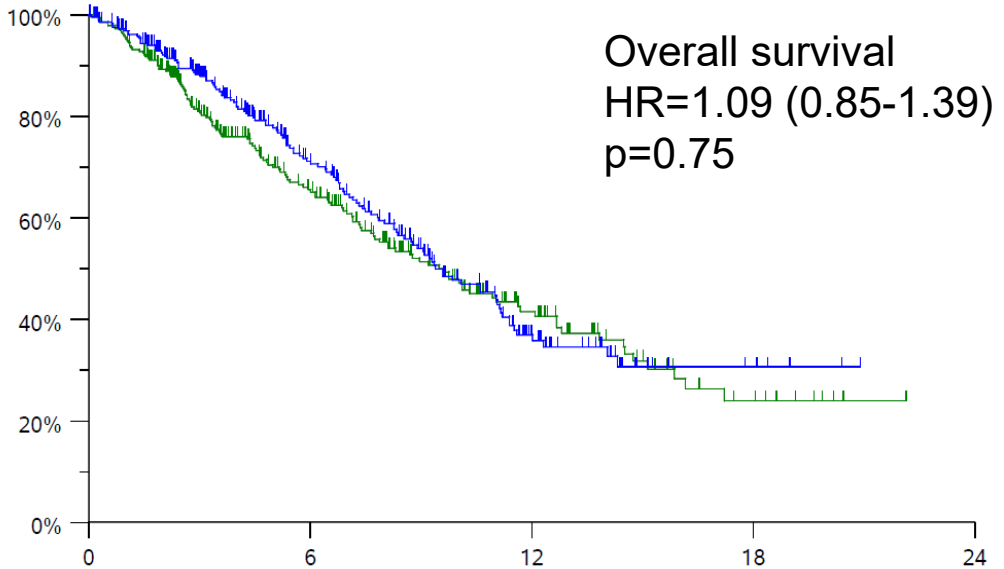
- First interim analysis at 40%/246 events in January 2025
- Second interim analysis at 60%/370 events in April 2025 – criteria for futility met
- Median follow-up for participants still alive: 5.2 months

Dragnev, et al. ASCO 2025, abstract LBA3671

Pragmatica-Lung
A real-world clinical trial for patients whose non-small cell lung cancer has returned after chemo- and immuno-therapy

Efficacy by histology

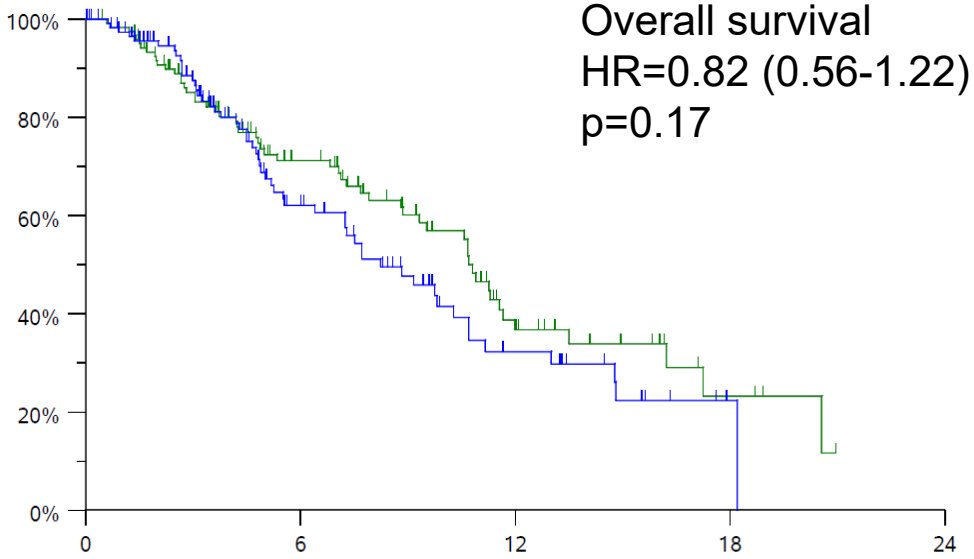
Non-squamous cell carcinoma



Overall survival
HR=1.09 (0.85-1.39)
p=0.75

	N	Deaths	Median in Months	95% Conf. Int.
Ramucirumab + Pembrolizumab	297	136	9.7	(7.7 - 11.6)
Standard of Care (Inv. Choice)	299	125	9.4	(8.4 - 11.1)

Squamous cell carcinoma



Overall survival
HR=0.82 (0.56-1.22)
p=0.17

	N	Deaths	Median in Months	95% Conf. Int.
Ramucirumab + Pembrolizumab	122	55	10.8	(8.9 - 12.0)
Standard of Care (Inv. Choice)	120	54	8.2	(6.4 - 10.7)

Pre-specified analysis by histology was included in the interim analysis plan

Dragnev, et al. ASCO 2025, abstract LBA8571

Pragmatica-Lung
A real-world clinical trial for patients whose non-small cell lung cancer has returned after chemo- and immuno-therapy

Key Takeaway Point

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Pragmatica-Lung sets a paradigm-shifting example in trial conduct that should be applied to future large randomized studies, including registrational intent

Pragmatic elements lead to faster protocol development and activation with less burden on research staff

OS with chemotherapy-free RP was not different from SoC, with a more favorable AE profile; longer follow-up may clarify if specific subsets derive differential benefit

Pragmatica-Lung achieved rapid accrual among representative population leading to generalizable results

Dragnev, et al. ASCO 2025, abstract LBA8671

S2302 Pragmatica-Lung Acknowledgments

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Yale SCHOOL OF MEDICINE
LUNG-MAP
SWOG CANCER RESEARCH NETWORK

Plan For the Talk

1. Evolution of Lung-MAP- A Master Protocol as a Public Private Partnership)

2. The Lung Pragmatica Trial

3. Thoughts for the Future

Lung-MAP Patient Testimonial

I said 'absolutely!' If I can go on the trial and help someone else, I would gladly do it … because they are fighting – excuse my language – a hell of a battle.

~ Austin A., on his response when asked to join Lung-MAP

Lung Map Meeting 2020 (days/hours before Covid lockdown)
Friends of Cancer Research, Washington DC

Thank You!

YaleNewHavenHealth Smilow Cancer Hospital | Yale CANCER CENTER A Comprehensive Cancer Center Designated by the National Cancer Institute | Yale SCHOOL OF MEDICINE | LUNG-MAP | SWOG CANCER RESEARCH NETWORK